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Health Effects Assessment for Chlordane

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HEALTH EFFECTS ASSESSMENT FOR CHLORDANE

U.S. Environmental Protection Agency
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16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

A q_1^* was determined for chlordane based on oral exposure.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with chlordane. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Chlordane. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-027. NTIS PB81-117384.

U.S. EPA. 1985. Drinking Water Criteria Document on Heptachlor, Heptachlor Epoxide and Chlordane. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. Final draft.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents in this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Data concerning chlordane exposure and cancer in human populations are limited and equivocal. Data concerning carcinogenicity in experimental animals following inhalation exposure are lacking.

Two oral cancer bioassays have been conducted (IRDC, 1973; NCI, 1977). U.S. EPA (1980b) used the IRDC (1973) data as evaluated by Reuber (1978), which showed an increased incidence of hepatocellular carcinoma in chlordane-exposed mice, to estimate cancer risk associated with chlordane exposure. A human q_1^* of 1.6075 $(mg/kg/day)^{-1}$ was computed. This risk assessment has been subjected to extensive peer review.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
LD_{50}	Median lethal dose
MED	Minimum effective dose
NOEL	No-observed-effect level
ppm	Parts per million
RNA	Ribonucleic acid
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of chlordane (CAS No. 57-74-98 for mixture; 5103-74-2 for cis isomer; 5103-71-9 for trans isomer) are as follows:

Chemical class:	pesticide
Moleculer weight:	406 (Callahan et al., 1979)
Vapor pressure:	1×10^{-5} mm Hg at 25°C (IARC, 1979)
Water solubility:	9 µg/ℓ at 25°C for technical grade and 56 µg/ℓ for cis:trans (75:25) chlordane (Verschueren, 1983; Deichmann, 1981)
Log octanol/water partition coefficient:	3.32 (Rao and Davidson, 1982)
BCF:	4700 for aquatic organisms with 1% lipid content (U.S. EPA, 1980b)
Half-lives in	
Water:	28-33 hours (Atlas et al., 1982)
Soil:	several years (Sanborn et al., 1977)

Information in the available literature is insufficient to estimate the half-life of chlordane in the atmosphere. Based on its reactivity in aquatic media (Callahan et al., 1979) and the reported presence of this compound in rainwater (Sanborn et al., 1977), however, both photolysis and physical removal mechanisms (wet and dry deposition) probably control the fate of atmospheric chlordane.

No pertinent information pertaining to the leachability of chlordane from soil to groundwater could be located in the available literature. The aqueous solubility and the octanol/water partition coefficient of this compound are such that significant leaching from soil is not expected to occur.

The long persistence time of this compound in soil may permit some leaching from soils, however, especially from soils with low adsorption for this compound.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Although quantitative data regarding the absorption of chlordane from the gastrointestinal tract of animals and humans are not available, the toxic effects observed after chlordane ingestion indicate that at least some absorption occurs. One male and one female Sprague-Dawley rat were given a single dose (0.05, 0.2 or 1.0 mg/kg) of [^{14}C]-HCS-3260, which is a highly purified chlordane preparation containing the cis- and trans-chlordane isomer in a 3:1 ratio (Barnett and Dorough, 1974). Within 7 days after treatment, 6% of the administered radioactive label was found in the urine of the female and 2% in the urine of the male. When cis- and trans-chlordane were given separately to female rats, 8.5 and 5%, respectively, of the administered radioactive label was eliminated in the urine. However, 33% of the administered radioactive label was excreted in the urine and 21% in the feces of a male rabbit within 2 days of receiving 25 ppm [^{14}C]-HCS-3260 in the diet. In cases where children (Curley and Garrettson, 1969; Aldrich and Holmes, 1969) have ingested chlordane, measurable quantities of chlordane have appeared in serum and fat several hours after the poisonings.

2.2. INHALATION

A peak concentration of radioactivity (~4% of the administered dose) appeared in the blood of Sprague-Dawley rats within 5 minutes of intratracheal administration of an unspecified amount of ^{14}C-chlordane (11,500 dpm/μg) in 20 μℓ ethanol as an aerosol spray (Nye and Dorough, 1976).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Ambrose et al. (1953a,b) exposed groups of three to five rats to food containing chlordane at levels from 10-1280 ppm for 400 days (Table 3-1). In males, increased liver weights were recorded at an exposure of 160 mg chlordane/kg diet. In females, increased liver weights were first observed in the group exposed to 10 mg chlordane/kg diet. Decreased body weight gain and increased severity of hepatic histopathological lesions were dose-related beginning at 160 mg/kg. Intracytoplasmic bodies were seen in livers at a dose level of 160 mg chlordane/kg diet. At higher dose levels, vacuolization and enlarged nuclei were seen in the liver.

DeLong and Ludwig (1954) treated an unspecified number of male and female rats with chlordane-contaminated dog pellets. The dose level of chlordane, calculated from amount of food consumption, was 1.2 mg/kg/day. After 5 months no histopathologic damage to lungs, heart, stomach, liver, kidneys, spleen or testes was reported. One treated rat had a kidney adenocarcinoma believed to be unrelated to chlordane exposure.

Shain et al. (1977) fed 19.5 mg/kg/day of chlordane to male Sprague-Dawley rats for 90 days. A randomly selected subgroup of 12 rats had significantly depressed body weight gain; another subgroup of 24 rats did not have depressed body weight gain. The purpose of this study was to investigate the effects of chlordane on the prostate gland. Nuclear, but not cytoplasmic, androgen binding sites were significantly increased, and RNA and DNA content and ventral prostate protein content were significantly decreased in the chlordane-treated rats.

Benign proliferative lesions in the liver were reported in 2% of the low dose (25 ppm) and 7% of the higher dose (50 ppm) groups of mice fed dietary chlordane for at least 36 weeks (Becker and Sell, 1979).

TABLE 3-1

Effects of Subchronic Oral Chlordane Exposure

Dose or Exposure (mg/kg diet)	Duration of Treatment	Duration of Experiment	Species/ Strain	Sex	Number Treated	Effects	Reference
0 10 20 40 80 160 320 640 1280	400 days	400 days	rat/NR	M/F M/F M/F M/F M/F M/F M/F M/F M/F	3-5	Increased liver weights, without additional symptoms, first occurred in females at a dose of 10 mg/kg diet. Increased liver weights accompanied by dose-related liver histopathology occurred in males at 160 mg/kg diet.	Ambrose et al., 1953a,b
0 1.2 mg/kg bw	5 months	5 months	rat/NR	M/F M/F	NR	No effects were reported.	DeLong and Ludwig, 1954
0 19.5 mg/kg bw	90 days	90 days	rat/ Sprague- Dawley	M	42 42	Decreased body weight gain. No significant weight changes in testes or ventral prostate. See text for additional information.	Shain et al., 1977
0 25 50	≥36 weeks	≥36 weeks	mouse/ C57BC 6N	M	200 NR NR	Benign proliferative lesions were reported to occur in the liver in the low-dose (2%) and high-dose (7%) groups.	Becker and Sell, 1979

NR = Not reported

3.1.2. Inhalation. Pertinent data regarding the subchronic toxicity of inhaled chlordane could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. Ingle (1952) treated groups of 20 rats/sex with chlordane in their food at a dose range of 5-300 mg/kg diet for 2 years (Table 3-2). Extensive histological data were reported, but organ and body weight data were not included. After 80 weeks of exposure at a dose level of 30 mg/kg diet, the animals developed tremors. At dose levels of $\geq$150 mg/kg diet, liver and kidney hypertrophy were detected, and histopathology was reported in the liver, kidney, lung, myocardium, adrenal gland and spleen.

In the IRDC (1973) study reviewed by Epstein (1976), groups of 100 mice/sex were exposed to 5, 25 and 50 mg of chlordane/kg diet for 18 months. The female mice appeared to be more sensitive than the male mice in this study, as indicated by the increased liver weights accompanied by hepatocytomegaly at a dose level of 5 mg/kg chlordane in the diet. Although hepatocytomegaly was present in male mice at this dose level, increased liver weight was not observed in males until they were exposed to the 25 mg/kg dose level. The highest dose level in this study (50 mg/kg diet) produced increased mortality in both sexes.

In the NCI (1977) study, both rats (50/sex/group) and mice (50/sex/group) were maintained on diets containing analytical grade chlordane for 80 weeks, followed by an observation period. Because the dose levels were changed during the experiment, the dosage listed in Table 3-2 is a TWA as calculated by the NCI (1977). Rats received higher dose levels in mg/kg bw than mice in this study. Female rats appeared to be more sensitive than male rats, as evidenced by increased mortality in females. High dose females, but not males, had tremors after 44 weeks of treatment.

TABLE 3-2

Effects of Chronic Oral Chlordane Exposure

Dose or Exposure (ppm)	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Treated	Effects	Reference
5 10 30 150 300	up to 2 years	2 years	rat/ Osborne- Mendel	M/F M/F M/F M/F M/F	20/20 20/20 20/20 20/20 20/20	Occasional hypertrophy of hepatocytes occurred at 5 mg/kg diet, but no other effects were observed. Slight tremors were present after 80 weeks at 30 mg/kg diet. Decreased growth rate, anorexia and tremors were seen in animals treated with 150 mg/kg diet; liver and kidney hypertrophy was present, as well as moderate to marked kidney, lung, myocardial, adrenal and spleen damage. At 300 mg/kg diet the animals died earlier and had severe liver, kidney, heart, adrenal, lung, myocardial and spleen damage.	Ingle, 1952
0 5 25 50	18 months	18 months	mouse/ CD-1	M/F M/F M/F M/F	33/45 55/61 52/50 39/37	Increased liver weight was significant at all dose levels for females and at 25 and 50 mg/kg diet for the males after 18 months of exposure. Survival was decreased for both males and females at 50 mg/kg diet. Hepatocytomegaly was observed in all treatment groups in both sexes.	Epstein, 1976
0 29.9 56.2	80 weeks	91 weeks	mouse/ B6C3F1	M M M	18 48 49	High-dose males and females had tremors at 20 weeks. Male mortality rate was significantly increased compared with controls in both the high- and low-dose treatment groups. No effect on mortality was seen in the females.	NCI, 1977
0 30.1 63.8	80 weeks	91 weeks	mouse/ B6C3F1	F F F	19 47 49		

TABLE 3-2 (cont.)

Dose or Exposure (ppm)	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Treated	Effects	Reference
0 203.5 407.0	80 weeks	109 weeks	rat/ Osborne- Mendel	M M M	6 34 31	Decreased body weights were seen in high-dose males and both dose levels of females. Tremors occurred in the high-dose females at 44 weeks. Dose-related increased mortality occurred in the females but not males.	NCI, 1977
0 120.8 241.5	80 weeks	109 weeks	rat/ Osborne- Mendel	F F F	10 43 32		
0.3 3.0 15.0 30.5	2 years	NR	dog	NR	NR	A review panel for WHO/FAO indicated that 3 mg/kg diet was a NOEL.	Wazeter, 1968

NR = Not reported

In a study by Wazeter (1968), dogs exposed orally to chlordane developed enlarged livers with histopathological changes. A scientific review panel of WHO/FAO examined this study and concluded that a dose of 3 mg/kg diet was a NOEL (Vettorazzi, 1975). No further information was available.

3.2.2. Inhalation. Pertinent data regarding the chronic toxicity of inhaled chlordane could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Ingle (1952) investigated the effect of chlordane-contaminated diets at dose levels of 5, 10, 30, 150 and 300 ppm on the fetus in utero and the newborn while nursing. Two female Osborne-Mendel rats from each dose level were mated after 24 and 48 weeks of chlordane exposure. No effect on fetal mortality and health or on litter size was reported. After birth, three pups remained with their chlordane-treated mothers, while three others were placed with foster mothers that had not been exposed to chlordane. Pups nursed by mothers exposed to chlordane levels of 150 and 300 mg/kg diet developed symptoms of toxicity, such as hyperexcitability, tremors, decreased body weight and death. Toxic symptoms developed in the pups that were nursed by mothers treated with chlordane-contaminated ($\geq$150 ppm) diets, whether or not they had been exposed in utero. However, the pups whose mothers were exposed to high levels of chlordane ($\geq$150 ppm) during pregnancy did not develop toxic symptoms when they were nursed by foster mothers exposed to low levels (5, 10 and 30 ppm) of chlordane.

3.3.2. Inhalation. Pertinent data regarding the teratogenicity or fetotoxicity of chlordane inhalation could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Intraperitoneal injection of phenobarbital in neonatal Sprague-Dawley rats reduced the LD_{50} of chlordane injected intraperitoneally (Harbison, 1975). Pretreatment of rats with chlordane potentiated the hepatocellular necrosis produced by carbon tetrachloride (Stenger et al., 1975). Male weanling Wistar rats (Boyd and Taylor, 1969) on a low-protein diet (3.5%) for 28 days had a much lower LD_{50} (137 ± 30 mg/kg bw) than a group of weanling rats that ate commercial rodent chow (LD_{50}=311 mg/kg bw).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Acute oral exposure to chlordane in humans (Curley and Garretson, 1969; Lensky and Evans, 1952; Aldrich and Holmes, 1969; Derbes et al., 1955; Dadey and Kammer, 1953) as a result of intentional or accidental poisoning causes CNS toxicity including, but not limited to, irritability, salivation, labored respiration, muscle tremors, convulsions and death. Pertinent data regarding the effects of chronic and subchronic human oral exposure to chlordane could not be located in the available literature; however, chlordane can cross the placenta (Curley et al., 1969; Wassermann et al., 1972; Zavon et al., 1969), and chlordane metabolites are found in milk (Savage et al., 1973; Strassman and Kutz, 1977). Neuroblastoma has been associated with perinatal exposure to chlordane (Infante et al., 1978).

4.1.2. Inhalation. Most inhalation exposure to chlordane occurs as work-related exposure either in the manufacturing or application of chlordane. Exposure to several chemicals in addition to chlordane often confounds evaluation of the human data. Aplastic and refractory megoblastic anemia, as well as acute stem cell, acute lymphoblastic and acute myelomonocytic leukemia, have been reported to result from chlordane exposure, primarily through inhalation (Infante et al., 1978; Klemmer et al., 1977; Furie and Trubowitz, 1976). A retrospective mortality study of 1403 white male workers employed for >3 months in the manufacture of chlordane and heptachlor indicated that the observed incidences of all types of cancer except lung cancer were less than expected (Wang and MacMahon, 1979). The increased incidence of lung cancer was not statistically significant. Insufficient population size, exposure duration and follow-up periods in this and other studies (Alvarez and Hyman, 1953; Ditraglia et al., 1981;

Fishbein et al., 1964; Princi and Spurbeck, 1951; Klemmer et al., 1977) preclude definitive conclusions regarding the effects of human occupational exposure.

4.2. BIOASSAYS

4.2.1. Oral. In the unpublished report by the IRDC (1973) reviewed by Epstein (1976), the liver lesions produced during chlordane treatment were originally diagnosed as preneoplastic lesions. A subsequent re-diagnosis of hepatocellular carcinoma was made by Reuber (1978) and other pathologists (Epstein, 1976). The results of this reevaluation are presented in Table 4-1.

In the NCI (1977) study, the dose levels were changed during the experiment for both mice and rats. The TWA dose levels calculated by the NCI (1977) are given in Table 4-1. Mice in the NCI (1977) study developed a dose-related increase in the incidence of hepatocellular carcinoma. As in the IRDC study (Epstein, 1976), the male mice appeared more sensitive. Rats in the NCI (1977) study developed miscellaneous neoplasms; these occurred spontaneously in the control groups as well as in the treated animals. The only significant dose-related increase in tumors was in fibrous histiocytomas in male rats. These tumors were discounted as biologically significant since the incidence is known to vary greatly. The incidence of thyroid tumors was not consistently significant or dose-related. One of the two hepatocellular carcinomas occurred in a low dose male; the other occurred in one of the pooled control animals.

Becker and Sell (1979) correlated elevated levels of alpha-fetoprotein with primary hepatocellular carcinoma in mice exposed for 36 weeks to diets containing 25 or 50 ppm of chlordane.

TABLE 4-1

Carcinogenicity of Chlordane by Oral Ingestion

Dose or Exposure (ppm)	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Treated	Target Organ	Tumor Incidence	Comments	Reference
0	550 days	550 days	mouse/	M	33	liver	3/33	Male mice appeared more	Epstein, 1976
5			CD-1	M	55		5/55	sensitive to the	
25				M	52		41/52	carcinogenic effects	
50				M	39		32/39	of chlordane in the liver.	
0	550 days	550 days	mouse/	F	45	liver	0/45		
5			CD-1	F	61		0/61		
25				F	50		32/50		
50				F	37		26/37		
0	80 weeks	91 weeks	mouse/	M	18	liver	2/18	Dose-related increase	NCI, 1977
29.9			B6C3F1	M	48		16/48	in the incidence of	
56.2				M	49		43/49	hepatocellular carcinoma	
0	80 weeks	91 weeks	mouse/	F	19	liver	0/19	was highly significant	
30.1			B6C3F1	F	47		3/47	($p<0.0001$) for both	
63.8				F	49		34/49	males and females.	
0	80 weeks	109 weeks	rat/	M	6	thyroid	0/6	Thyroid tumors included	NCI, 1977
203.5			Osborne-	M	34		6/34	follicular cell adenoma	
407.0			Mendel	M	31		11/31	and carcinoma as well as C-cell adenoma and	
0	80 weeks	109 weeks	rat/	F	10	thyroid	3/10	carcinoma. Only two	
120.8			Osborne-	F	43		7/43	hepatocellular carcinomas	
241.5			Mendel	F	32		16/32	were observed.	

4.2.2. Inhalation. Pertinent data regarding the inhalation carcinogenicity of chlordane could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Chlordane did not cause reverse mutations in nine strains of Salmonella typhimurium or in two strains of Escherichia coli with or without metabolic activation (Probst et al., 1981; Gentile et al., 1982); unscheduled DNA synthesis in rat, mouse or hamster primary hepatocyte cultures (Probst et al., 1981; Maslansky and Williams, 1981); or dominant lethal mutations in CD-1 mice following intragastric or intraperitoneal administration (Arnold et al., 1977). Positive results were obtained for mitotic gene conversion assays in Saccharomyces cerevisiae only after metabolic activation (Gentile et al., 1982), and for unscheduled DNA synthesis in SV-40 transformed human fibroblasts only in the absence of metabolic activation (Ahmed et al., 1977).

4.4. WEIGHT OF EVIDENCE

Oral exposure to chlordane was associated with hepatocellular carcinoma in male and female CD-1 and B6C3F1 mice (Epstein, 1976; NCI, 1977), but liver tumors in mice may occur spontaneously at a high rate and their validity as an indicator of potential human carcinogenicity has not been established. IARC (1982) concluded that the evidence for the carcinogenicity of chlordane in humans and for the mutagenicity of chlordane in short-term tests was inadequate; the evidence for the carcinogenicity of chlordane in animals was considered limited. Applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), chlordane is most appropriately classified as a Group C chemical.

5. REGULATORY STANDARDS AND CRITERIA

A tolerance of 0.3 mg/kg has been established by the U.S. EPA (Federal Register, 1976) for residues of chlordane in or on ~50 fruit and vegetable crops (Code of Federal Regulations, 1976). The ACGIH (1983) has adopted TLV values only for percutaneous chlordane exposure.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Chlordane is a chemical for which a carcinogenic potency has been computed and that may be carcinogenic in humans. It is, therefore, inappropriate to calculate an oral or inhalation AIS for chlordane.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Chlordane is a chemical for which a carcinogenic potency has been computed and that may be carcinogenic in humans. It is, therefore, inappropriate to calculate an oral or inhalation AIC for chlordane.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The data from the IRDC (1973) study, reported by Epstein (1976) and diagnosed by Reuber (1978), on the development of hepatocellular carcinoma in male B6C3F1 mice exposed orally to chlordane was used by the U.S. EPA (1980b) to derive a q_1^* for humans of 1.6075 $(mg/kg/day)^{-1}$. This study resulted in greater incidences at lower doses than did the NCI (1977) bioassay in mice and, therefore, would result in a more conservative q_1^*, 1.607 $(mg/kg/day)^{-1}$. The data upon which this determination is based are presented in Appendix A.

6.3.2. Inhalation. Data were not available for estimation of carcinogenic potency following inhalation exposure.

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APPENDIX A

Cancer Data Sheet for Derivation of q_1^*

Compound: Chlordane

Reference: Epstein, 1976

Species, Strain, Sex: Mice, CD-1, male

Body weight: 0.041 kg (measured)

Length of exposure (le) = 546 days

Length of experiment (Le) = 546 days

Lifespan of animal (L) = 546 days

Tumor site and type: liver, carcinoma

Route, vehicle: oral, diet

Experimental Doses or Exposures (ppm)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	3/33
5	0.65	5/55
25	3.25	41/52
50*	6.5*	32/39*

*High-dose data are dropped to comply with goodness of fit.

Unadjusted q_1^* from study = 1.3448×10^{-1} $(mg/kg/day)^{-1}$
Human q_1^* = 1.607 $(mg/kg/day)^{-1}$

APPENDIX B

Summary Table for Chlordane

	Species	Experimental Dose/Exposure	Effect	q_1^*	Reference
Inhalation					
AIS				ND	
AIC				ND	
Carcinogenic potency				ND	
Oral					
AIS				ND	
AIC				ND	
Carcinogenic potency	mice	5, 25 and 50 ppm	hepatocellular carcinoma	1.6075 $[mg/kg/day]^{-1}$	Epstein, 1976; U.S. EPA, 1980b

ND = Not derived